Associations among Antioxidant Intake and Cardiovascular Health in Women with Chronic Hypertension

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Abstract

One in three American women have hypertension, a disease with modifiable risk factors. One preventative measure is a diet high in fruits and vegetables. Occurring naturally in fruits and vegetables are antioxidants vitamin C and vitamin E. We aimed to determine if higher intake of vitamin C and/or E was associated with lower blood pressure and improved vascular function, thus providing preliminary data regarding the potential effectiveness of dietary antioxidant intake on cardiovascular health among women. Using a cross-sectional design, 11 women were enrolled in the primary study. Participants completed the diet history questionnaire (DHQ), assessing nutrient intake over the previous 30 days. Blood pressure was measured based on standard procedures. Reactive hyperemic index (RHI) determined vascular dysfunction, with lower RHI indicative of worse function (EndoPAT, Itamar Medical; Israel). Descriptive statistics were used to determine sample characteristics. Association among dietary vitamin C and E intake, systolic (SBP) and diastolic (DBP) blood pressure, and RHI were examined using Pearson's correlations (α=0.05). Participants were ages 35-60, with an average BMI of 37.5 (SD=8.6). Average daily vitamin C and E intake was 95.6 mg (SD=46.2) and 12.3 IU (SD=6.6), respectively. The average SBP was 142.1 (SD=19.0) and DBP was 82.4 (SD=9.7). Average RHI was 1.57 (SD=0.5). Vitamin C and E intake were significantly positively associated with one another (r=0.7085, p=.015). However, vitamin C intake was not significantly associated with SBP (r=-0.2567, p=.446), DBP (r=0.0878, p=.797), or RHI (r= 0.2975, p=.374). Associations among vitamin E intake and SBP (r=-0.2932, p=.382), DBP (r=0.0137, p=.968), and RHI (r=0.5154, p=.105) were not statistically significant. Although it is not statistically significant, there was a trend for increased vitamin C and E intake in lowering SBP and improving vascular function. With the

small sample, future studies exploring the correlation between dietary vitamin C and E intake on BP/vascular function in a larger population may identify effects of these antioxidants on cardiovascular health.

Chapter I: Statement of the Problem

Introduction

Cardiovascular health is a significant problem in the United States that has increased in prevalence over the years. Of these diseases, high blood pressure is one of the most common. According to the Center of Disease Control and Prevention, about 1 of 3 adults - or about 70 million people - have high blood pressure, otherwise known as hypertension (Nwankwo, Yoon, Burt & Gu, 2013). Additionally, hypertension is a risk factor for heart disease and stroke, two of the leading causes of death in women.

Background of the Problem

There are several identified modifiable risk factors for cardiovascular disease around a framework of wellness and self-care. The American Heart Association's 2011 Guidelines for preventing cardiovascular disease in women currently recommend smoking cessation, DASH-like diet, regular physical activity and weight management for the prevention of cardiovascular disease in women (Mosca, Benjamin, Berra et al., 2011). The diet should be rich in fruits and vegetables, whole-grain and high-fiber foods, fish twice a week with limited intake of saturated fat, cholesterol, alcohol, sodium and sugar (Mosca, Benjamin, Berra et al., 2011). This diet intervention is useful and effective in preventing cardiovascular disease.

Occurring naturally in fruits and vegetables are substances known as antioxidants. Antioxidants, such as vitamin C and vitamin E have been reported to be associated with less oxidative stress and reduced cardiovascular disease risk (Hodgson, Croft, Woodman et al., 2014). However, the research supporting reduced cardiovascular risk through dietary antioxidant intake is inconclusive and the beneficial effects of the specific vitamins on cardiovascular events and health have yet to be established, particularly among women with current hypertension.

Purpose of the Study

Current research findings show conflicting viewpoints of whether or not antioxidants have a positive impact on the cardiovascular system, specifically blood pressure and vascular function. Additionally, the current American Heart Association Guidelines for preventing cardiovascular disease in women do not recommend a diet high in antioxidants (Mosca et al., 2011). Therefore, the purpose of this pilot study was the determine the association of dietary vitamin C and vitamin E intake with blood pressure and vascular function, thus providing preliminary data regarding the potential effectiveness of dietary antioxidant intake on cardiovascular health among women.

Conceptual Frame of Reference (Theory)

Pender's Health Promotion Model, which posits that raised consciousness related to health promotion behaviors is key to achieving positive health outcomes, served as the theoretical framework for this study (Pender, Mudaugh & Parsons, 2002). Pender explains this theory as a guide for discovering complex physiological processes, which motivates individuals to change their behavior and leads them to promotion of health and hygiene (Sharifirad, Kamran, Azadbakht et al., 2015), additionally assuming the person takes an active role to maintain healthy behaviors. Huessein, El Salam & Amr (2016) conducted a study to assess the effect of application of Pender's Health Promotion Model on management of hypertension among adults in a rural area and found that this model, along with nursing educational intervention, was successful in improving knowledge, lifestyle behaviors and blood pressure.

Research Questions

We aimed to address the following questions:

(1) Among women with hypertension, is a diet high in vitamin C and vitamin E associated with lower blood pressure?

(2) Among women with hypertension, is a diet high in vitamin C and vitamin E associated with improved vascular function?

Definitions of Terms

In this study, hypertension is defined as having a systolic pressure of 140 mmHg or higher and a diastolic pressure of 90 mmHg or higher. Additionally, vascular function is determined by reactive hyperemic index (RHI) measured by EndoPat (Itamar Medical; Israel), with lower RHI indicative of worse function and an RHI <1.67 indicative of dysfunction. We define vitamin C levels in terms of milligrams (mg) and vitamin E levels in terms of international units (IU) per day.

Chapter II: Review of Literature

Introduction

A number of studies have shown an influence of diet on cardiovascular health. The purpose of this literature review was to examine and assess the evidence regarding the association between dietary antioxidant intake and hypertension. This review of literature was conducted using three search engines: Pubmed, CINHAL and Google Scholar. Using the key words 'diet', 'hypertension', 'cardiovascular disease', 'antioxidants', 'DASH diet', 'Mediterranean diet', 'Vitamin C', 'Vitamin E', and 'endothelial dysfunction,' several articles were identified. Articles range from 1997 to 2016, keeping in mind that those more current represent progressive advances. Some of the older articles contain background knowledge expanded on in more recent publications. Articles review how the DASH diet and the Mediterranean diet affect cardiovascular health, specifically focusing on dietary/supplemental antioxidant intake and cardiovascular disease. A total of 55 articles were reviewed, with 17 being selected and considered for this review. The articles were selected based on their relevance to the study and research questions. Nine of the 17 articles are from the last ten years (2007- 2017). Articles provide evidence regarding the effect of the DASH diet and the Mediterranean diet on cardiovascular health, pathophysiology of endothelial dysfunction, antioxidants role in cardiovascular health, and treatment of endothelial dysfunction.

Heart Healthy Diets

Diet is a key modifiable risk factor in the prevention and risk reduction of heart disease. The Mediterranean style diet and the DASH diet have been shown to lower risk of coronary heart disease and lower likelihood of developing hypertension (Bhupathiraju & Tucker, 2011). The review of literature included the components for the DASH and Mediterranean diets, ultimately focusing on antioxidants vitamin C and vitamin E and their effects on cardiovascular health.

DASH diet

The DASH diet stands for Dietary Approaches to Stop Hypertension. This eating plan is designed to help prevent and treat hypertension. The DASH diet includes foods that are low in saturated fat, total fat, and cholesterol, and high in fruits, vegetables, and low fat dairy foods. Individuals who follow the DASH diet consume less red meat, sodium (salt), sweets, added sugars and sugar- containing beverages and consuming more whole grains, poultry, fish and nuts (Appel et al., 2006). The DASH diet is recommended by the American Heart Association in managing hypertension. Findings from Appel’s clinical trial suggested that a diet rich in fruits, vegetables and low-fat dairy foods with reduced saturated and total fat could substantially lower blood pressure (Appel et al., 1997). Since then Appel has completed numerous studies on the effects of the DASH diet on hypertension. In 2006, the American Heart Association reported reduced salt intake, increased potassium intake and consumption of dietary patterns based on the “DASH diet” have emerged as effective strategies in lowering blood pressure (Appel et al., 2006). Further, a recent systematic review reported that 17 randomized control trials evaluating the DASH diet were conducted through 2013. Findings demonstrated the DASH diet significantly lowered blood pressure in adults even thought there were variations in intervention duration, sample size, intervention type, study design and participants’ conditions across studies (Saneei, Salehi-Abargouei, Esmaillzadeh & Azadbakht, 2014). The collective evidence supports the use of the DASH diet for the prevention and management of hypertension.

Mediterranean Diet

The Mediterranean style diet has also been shown to lower the likelihood of developing hypertension. The Mediterranean style diet includes a dietary pattern that emphasizes intake of vegetables, fruit, and whole gains; including low-fat dairy products, poultry, fish, legumes, and mom tropical vegetable oils and nuts, and limits intake of sweets, sugar-sweetened beverages, and red meats (Nissensohn, Román-Viñas, Sánchez-Villegas, Piscopo & Serra-Majem, 2016). In a systematic review, 6 trails encompassing 7,000 individuals were analyzed with results showing that following a Mediterranean diet for at least one year reduced both the systolic and diastolic blood pressure levels in individuals with normal blood pressure or mild hypertension (Nissensohn et al., 2016). This study shows the beneficial effects of the Mediterranean diet, however it does not establish its general effectiveness. In a more recent systematic review, the Mediterranean diet participants experienced a significant incremental reduction is diastolic, but not systolic blood pressure (Gay, Rao, Vaccarino & Ali, 2016). There is evidence for the heart healthy benefits of the Mediterranean diet in the reduction of blood pressure, through the specific dietary components have not been identified.

Factors within Heart Healthy Diets

Vitamin C and Vitamin E

Two micronutrients that are represented in both the DASH diet and the Mediterranean diet are the antioxidants vitamin C and vitamin E. Vitamin E is the key fat-soluble antioxidant in the human body that functions in both plasma and low density lipoprotein (LDL) as a chain-breaking antioxidant and this “oxidation modification hypothesis of LDL” supports a biological role for vitamin E in preventing cardiovascular disease (Bhupathiraju & Tucker, 2011). Common sources of vitamin E are nuts, seeds, vegetable oils and green leafy vegetables. Vitamin E is also available as a supplement. Vitamin C, also known as ascorbic acid, is also an antioxidant. Because of the role as a free radical scavenger, vitamin C has been hypothesized to have a preventative role in cardiovascular disease (Bhupathiraju & Tucker, 2011). Common sources of vitamin C include many fruits -cantaloupe, citrus fruits and juices (orange, grapefruit juice), mango - which are recommended to be increased in consumption in decreasing risk for hypertension. The American Heart Association recommendations do not include antioxidant supplements (i.e. vitamin E or C) for the primary or secondary prevention of cardiovascular disease (Mosca et al., 2011). However, there have been trials studying the effects of vitamin C and vitamin E supporting a decreased risk in development of cardiovascular disease.

Studies Examining Effects of Vitamin C and Vitamin E on Cardiovascular Health

The American Heart Association concluded that the scientific data did not justify the use of antioxidant vitamin supplements for cardiovascular disease risk reduction (Kris-Etherton, Lichtenstein, Howard, Steinberg & Wiztum, 2004). Since 2004, there have been studies conducted that provide evidence for vitamin C and vitamin E and their impact in reducing cardiovascular disease risk. Evidence supports that a diet with increased intake of vitamin E and vitamin C contributes to the lowering of blood pressure by reducing oxidative stress and improving endothelial function (Hodgson, Croft, Woodman et al., 2014). In a randomized, double-blind, placebo-controlled trial it was found that vitamin C alone reduces systolic blood pressure compared to placebo (Ward, Hodgson, Croft et al., 2005). A Danish study with more than 100,000 people concluded that high intake of fruit and vegetables was associated with a fifteen percent lower risk of developing heart disease. Additionally, the researchers suggest that the reduced cardiovascular risk is related to high vitamin C concentrations from the fruits and vegetables (Kobylecki, Afzal, Smith & Nordestgaard, 2015). The literature supports associations among vitamin C, vitamin E, and cardiovascular disease. However, this research is inconclusive and there are gaps that need to be filled to conclude the generalized effectiveness of these antioxidants on cardiovascular health.

Pathophysiology of Endothelial Dysfunction on Cardiovascular Health

Endothelial function plays a crucial role in maintaining good cardiovascular health. Endothelial dysfunction can be defined as reduced bio-availability of nitric oxide (NO), which causes an impairment of endothelium-dependent vasodilation (Itamar Medical; Israel). Impaired arterial dilation puts a person at risk for the development of cardiovascular disease, including hypertension. Loss of endothelium-dependent vasodilation, otherwise known as endothelial dysfunction, in both adults and children has been associated with smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, a family history of premature atherosclerotic disease, obesity, elevated C-reactive protein, and chronic systemic infection (Widlansky, Gokce, Keaney & Vita, 2003). Thus, Lerman & Zeiher (2005) identified endothelial dysfunction as the "ultimate risk of the risk factors," alluding to to the underlying foundation of cardiovascular disease.

Antioxidant Treatment of Endothelial Dysfunction

Studies have shown that oxidative stress is a central cause of endothelial dysfunction in atherosclerosis (Widlansky et al., 2003), which has led to numerous studies addressing antioxidant treatment of endothelial dysfunction. Heitzer et al. (1999) found in their double-blind, placebo-controlled study that long-term vitamin E supplementation improves endothelium-dependent relaxation in forearm resistance vessels of hypercholesterolemic smokers, suggesting the beneficial effect of vitamin E on endothelial dysfunction. However, there are conflicting studies that argue that vitamin E does not improve endothelial dysfunction (Widlansky et al., 2003). Additionally, a pilot study of 15 people showed vitamin C improved impaired endothelium, flow-dependent dilation in patients with chronic heart failure as a result of increased availability of nitic oxide (Hornig, Arakawa, Kohler & Drexler, 1998). Although there is data to support the beneficial effects of these vitamins, it is outdated and limited due to the presence of co-morbid conditions in the trials.

Conclusion

Overall, the evidence gathered reports that both the DASH diet and Mediterranean diet aide in hypertension management. A component of both of these diets, antioxidants, specifically vitamin C and E, have shown an association with cardiovascular disease. Additionally, we have seen the effects these vitamins can have on endothelial dysfunction. However, there has not been conclusive evidence in recent, up-to-date, studies that can confirm this hypothesis and thus poses a gap in the literature. This study, which will examine the diet of women with chronic hypertension, aims to determine if there is a correlation between antioxidants and cardiovascular health, specifically blood pressure and vascular function.

Chapter III: Methodology

This study was a secondary analysis, with the parent study designed to identify a potential association between DNA methylation in peripheral blood cells, diet, activity and pregnancy history with blood pressure and/or vascular function. This chapter serves to describe the research design, participants, data collection procedures, data collection instruments, analytic plan and protection of human subjects.

Research Design

The parent study was a pilot study that used an observational design and convenience sampling. The purpose of this study was to identify distinct epigenetic patterns of DNA methylation associated with preeclampsia (PE) that underlie the future development of hypertension and to determine the implication on responses to moderators and therapeutic interventions in the management of chronic hypertension. The study included data collected from chart review and questionnaires which served as the foundation for the questions posed in this secondary analysis.

Participants

To recruit participates, appropriate candidates were identified by a study-investigator through review of medical records at a health system in the northern central U.S.. Advertisements were also placed in the community and clinical settings where potential participants are likely to be. After identifying appropriate candidates based on eligibility criteria through an initial screen, participants were invited to participate in the study by a member of the research team. The team recruited women diagnosed with chronic hypertension, aged 35-60 years, with or without a history of preeclampsia. These participants were recruited from an internal medicine local community. Criteria for inclusion were as follows: English speaking, female gender, history of prior pregnancy (normotensive or complicated by preeclampsia), established diagnosis of chronic hypertension, current treatment of chronic hypertension, age 30-60. The age range was limited to reduce the likelihood of co-morbid conditions. Exclusion criteria included: pregnant women, presence of comorbid conditions that influence cardiovascular health (i.e. autoimmune, diabetes, congenital cardiac anomalies).

Participants were scheduled for a single visit to complete data collection. If the participant offered verbal interest and they met the inclusion criteria, they were informed of the expectations of participation, the risks and discomforts, adverse reactions, right to withdraw from the study at any time and the confidentiality of the study. Participants were given this information orally and in writing with time to read over the information and ask questions. If still interested in participation, they were asked to sign the consent form and a copy was given to them for their records. Original consent forms were kept locked in a cabinet in a secure location.

Data Collection Procedures

In a private location at the research site, data, including demographic information, medical history, and physical activity report, was collected using an investigator developed questionnaire. Dietary intake data was collected. Vascular function was measured and blood pressure recorded. Medical record data retrieval was abstracted from the records of the primary care provider co-investigator.

Data Collection Instruments

Dietary intake was measured using the Diet History Questionnaire (DHQII, Version 2.0). The DHQII contains 134 food items and 8 dietary supplement questions based on recent National Health and Nutrition Examination Surveys data. This survey is freely available and was delivered electronically to the patient. Participants selected, based on portion sizes, foods representing dietary intake and dietary supplements over the past 30 days. Analysis was conducted using the Diet*Calc Analysis Program, Version 1.5.0. National Cancer Institute, Applied Research Program.

Participants' vascular function was measured using an Endo-PAT2000 (Itamar Medical; Israel). Testing was conducted in a quiet environment with no loud noises or distractions. All jewelry, watches and rings were removed. Participants were placed in the supine position. Blood pressure was measured from the dominant arm at least 5 minutes before study. The blood pressure cuff for occlusion was applied to patient's non-dominant arm. EndoPat probe was placed on the index finger and positioned to assure the fingers remained separated during the test. Test then began and took approximately 20 minutes to complete.

Analysis

As stated previously, blood pressure was measured based on standard procedures. The final concluded result of the EndoPAT test is the Reactive Hyperemia Index (RHI). This is a ratio of the post- to pre occlusion peripheral arterial tone amplitude of the tested arm, divided by the post- to- pre occlusion ratio of the control arm. Bonetti et al.'s study provides the threshold for a good EndoPAT result being an RHI of 1.67 and above. Descriptive statistics were used to determine sample characteristics. Association among dietary vitamin C and E intake, systolic (SBP) and diastolic (DBP) blood pressure, and RHI were examined using Pearson's correlations (α=0.05).

Protection of Human Subjects

Participants were assigned a unique code to prevent identification. Linkages of patient identification with a unique code were secured by the PI in a password secured, confidential computer file. This linkage was separate from data files. No individual data was reported. Data is reported in aggregate form. Consent forms will be kept in a secure location separate from data files. Both the research data and consent forms will be kept for a minimum of three years following completion of the study. The consent forms will be professionally shredded after the three-year minimum. Upon complete collection of data, the PI maintaining linkage data will shred all documents.

Chapter IV: Results

Sample Descriptive Statistics

In this secondary analysis, we analyzed the sample used in the primary study which included 11 English- speaking women, ages 35-60 with a history of prior pregnancy, chronic hypertension and current treatment of chronic hypertension. As shown in Table 1, the average age of participants was 53 years and 55% percent had graduated college. There was an average BMI of 37.53, with every participant overweight or obese. Average daily dietary vitamin C intake was 95.63 mg and average daily dietary vitamin E intake of 12.30 IU. Average systolic blood pressure (SBP) was 142 mmHg, average diastolic blood pressure (DBP) 82 mmHg and average reactive hyperemic index (RHI) 1.57.

Table 1. Descriptive Statistics (n= 11)

Table 1. Sample Descriptive Statistics (N=11)	
Age (Mean, (SD))	53 (9)
Education (%)	
≤ Some college	45%
≥ Bachelor's degree	55%
BMI (Mean, (SD))	37.5 (8.6)
Vitamin C intake [mg/day] (Mean, (SD))	95.6 (46.2)
Vitamin E intake [IU/day] (Mean, (SD))	12.3 (6.6)
Systolic Blood Pressure (Mean, (SD))	142 (19)
Diastolic Blood Pressure (Mean, (SD))	82 (10)
Reactive Hyperemic Index (Mean, (SD))	1.57 (0.46)

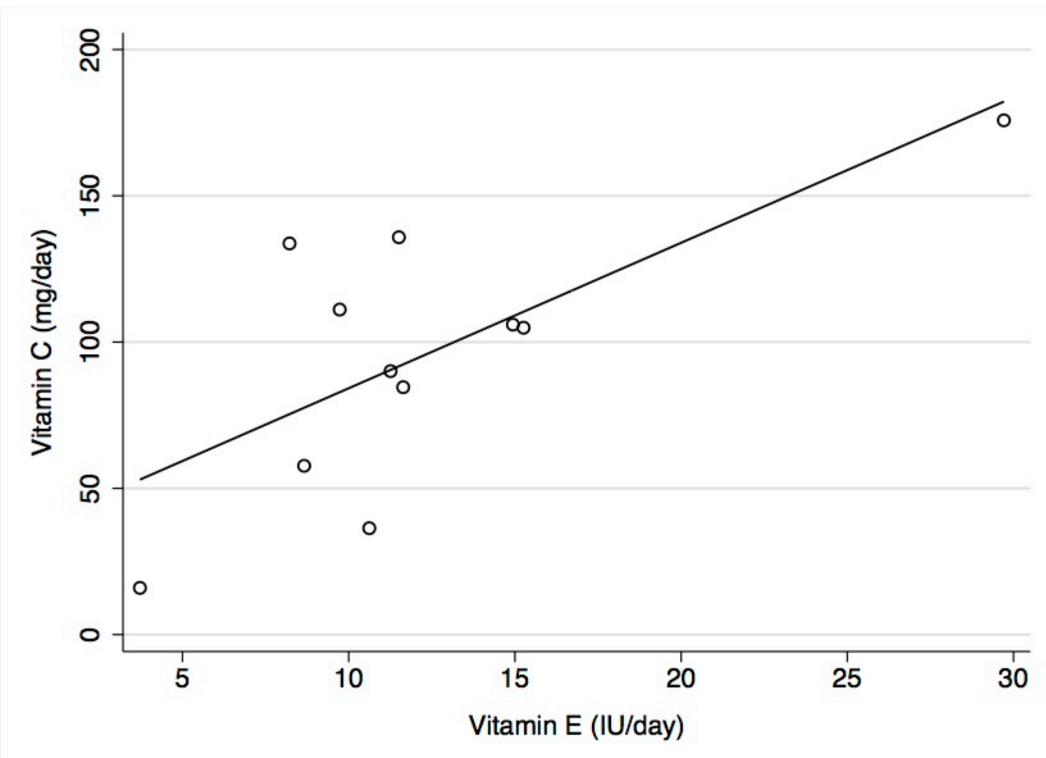
Correlations are presented in Table 2. Associations among dietary vitamin C and vitamin E intake, SBP and DBP, and RHI were examined using Pearson's correlations (α=.05). Vitamin C and E intake were significantly positively associated with one another (r=0.7085, p=.015; Figure 1). No other correlations were significant.

Table 2. Correlation table

Table 2. Correlation Matrix					
	Vitamin C	Vitamin E	SBP	DBP	RHI
Vitamin C	1.00	--	--	--	--
Vitamin E	.71***	1.00	--	--	--
SBP	-.26	-.29	1.00	--	--
DBP	.09	.01	-.11	1.00	--
RHI	.30	.52*	.004	-.48	1.00

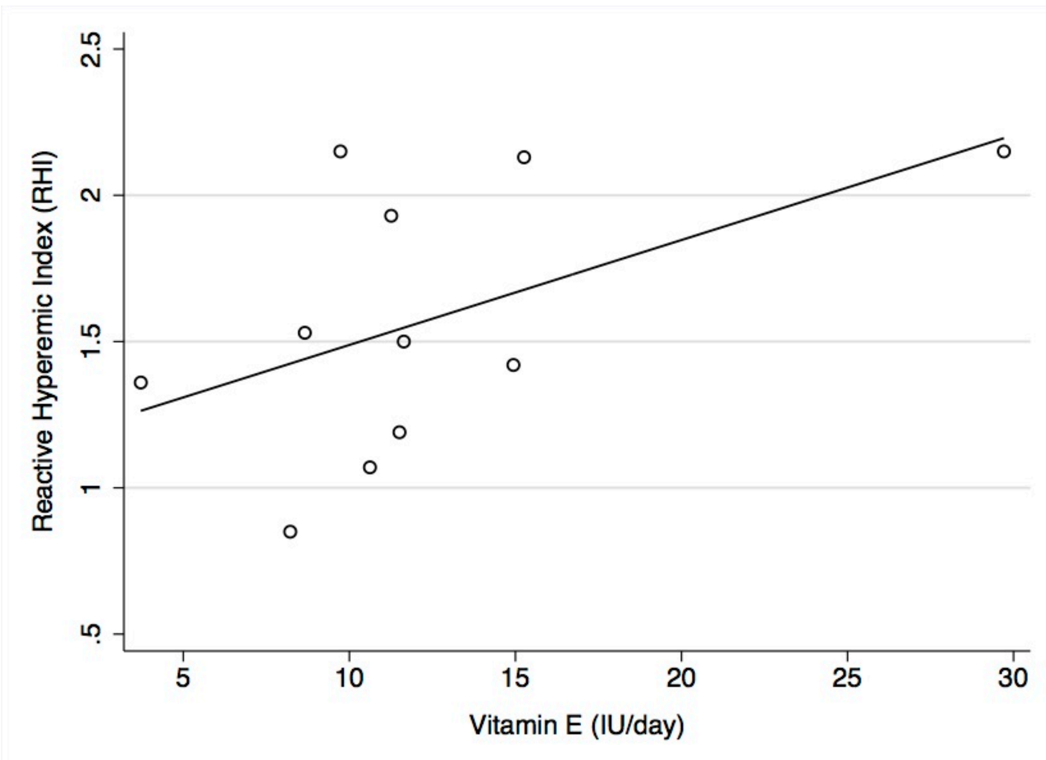
Note: Pearson's *r* presented; *p < .15, **p < .10, ***p < .05

Figure 1. Vitamin E and Vitamin C intake



Vitamin C intake was not significantly associated with SBP (*r*=-0.2567, p=.446) or DBP (*r*=0.0878, p=.797). Associations among vitamin E intake and SBP (*r*=-0.2932, p=.382) and DBP (*r*=0.0137, p=.968) were not statistically significant. Vitamin C intake was not significantly associated with RHI (r= 0.2975, p=.374). A positive association was noted between vitamin E intake and RHI (r=0.5154), although the relationship was not statistically significant (p=.105; Figure 2).

Figure 2. Vitamin E and RHI



Chapter V: Conclusions and Recommendation

Conclusions

In summary, we found no significant associations between dietary vitamin C and E intake and blood pressure or vascular function. We did however find a trend displaying greater vitamin C and vitamin E dietary intake with lower SBP. The literature supports that there is an association between vitamin C and vitamin E and lower risk for cardiovascular disease, but our findings do not bridge the gap that posits regarding their potential beneficial effects. A further study isolating these vitamins within a large population would be needed to assess effects of vitamin C and vitamin E dietary intake or supplementation on cardiovascular health among women with chronic hypertension. In addition to that, greater vitamin C and vitamin E intake showed a trend for better vascular function by improved RHI scores. This was consistent with the literature found, which displayed the beneficial effects of vitamin E and vitamin C on endothelial dysfunction. Although our results were not significant, we see the trends for vitamin C and E intake for lower SBP and better vascular function, which suggests future studies in a larger population could potentially identify the significance of these antioxidants on blood pressure and endothelial dysfunction.

Limitations

Limitations of the study include a small sample size and minimal diversity in participants. The study's sample include all Caucasian women. Additional exclusion criteria included pregnant women and the presence of a comorbid condition that may influence cardiovascular health (i.e., autoimmune, diabetes, congenital cardiac anomalies). These limitations may decrease the ability to generalize the results to other racial groups and culture populations and those with the stated comorbidities.

Recommendations

After analyzing the results from this study, it appears that increased vitamin C and vitamin E intake showed a trend for lowering SBP. Additionally, increase vitamin C and vitamin E intake showed a trend for improved vascular function. Future studies exploring the correlation between dietary vitamin C and vitamin E intake on blood pressure and vascular function in a larger population would be recommended as they may identify the effects of these antioxidants on cardiovascular health.

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